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LIVERPOOL HOSPITAL FOR CONSUMPTION

Research Laboratory Reports

I.—ON THE

VALUE OF SOME MODERN METHODS OF DIAGNOSIS AND TREATMENT IN TUBERCULAR DISEASES

BY

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[*Reprinted from The Liverpool Medico-Chirurgical Journal, January* 1908]

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PRINTED BY
NEILL & CO., LTD., BELLEVUE, EDINBURGH
1908

ON THE VALUE OF SOME MODERN METHODS OF DIAGNOSIS AND TREATMENT IN TUBERCULAR DISEASES.

By

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The successful treatment of consumption and other tubercular diseases depends to a very large extent on their early recognition. This fact is now so generally recognised that any improvements in our means of diagnosis are readily welcomed, and their value eagerly tested. The time-honoured methods of examination may first be briefly mentioned.

Family History is important as evidence of the suitability of the soil for the growth of the tubercle bacillus, but even more as evidence of exposure to infection. It is particularly important to ascertain whether the patient has been in close and intimate contact with a known consumptive within the previous few months.

Previous History.—Any history of previous chest disease is important, more especially attacks of pleurisy. Recurrent attacks of pleurisy are exceedingly suggestive. Chronic bronchitis of long standing often proves to be tuberculous on careful examination.

Symptoms.—Of special importance in early diagnosis are:—

Hæmoptysis: All cases of hæmoptysis where no local cause can be found should be treated as phthisis, even where no other evidence can be discovered.

Impaired working capacity: often a very early symptom.

Pain: especially when referred to the shoulder and scapular region.

Dyspepsia: often present early.

Tachycardia: may occur before any other symptom.

Physical signs: are of the greatest value, but it must be remembered that frequently the disease is far advanced before they are clear and unmistakable. Careful examination of the apices is not sufficient. Routine examination of the whole thorax reveals, more frequently than is generally supposed, the existence of unmistakable signs in abnormal situations. Chronic local inflammation in the lungs is usually due to the tubercle bacillus, but a patient can frequently be proved to have consumption where there are no physical signs at all, or where physical examination reveals only a general bronchitis.

Examination of Sputum.—The demonstration of tubercle bacilli in the sputum may, in practice, be taken as conclusive evidence of consumption, and there is no other evidence of equal value. A negative result of the examination, however, by no means disproves the existence of consumption, though it makes it less probable. The value of a negative result depends entirely on the care with which the examination is made. In doubtful cases the following method should be employed.

The patient should be directed to expectorate every morning for a week into a large wide-mouthed bottle. The collected sputum is then poured on to a large glass plate, and a likely piece is picked up with forceps and smeared in a thin film on a slide. This is fixed in saturated corrosive sublimate and stained in the usual way with carbolfuchsin and methylene blue. A convenient method of applying the fuchsin is by heating it to boiling in a test-tube, and pouring it on to the slide through a filter. Staining is complete when the liquid cools. Should one slide fail to show bacilli, six different portions of the sputum should be examined. Should these still show nothing, the whole mass of sputum should be placed in a wide-mouthed bottle, which is then filled up with 1 per cent. hydrochloric acid to which half a teaspoonful of powdered pepsin is added. (1 per cent. HCl may be made by mixing 3 c.c. of strong acid with 97 c.c. of water.) The bottle is corked, thoroughly shaken up, and placed in an incubator at blood-heat for twenty-four hours. At the end of that time the bottle will contain a clear fluid with debris at the bottom, consisting of tubercle bacilli, elastic fibres, and the nuclei of cells. Some of this debris is then taken in a capillary pipette, spread on a slide, and stained in the usual way.

By this method bacilli can often be detected which can be demonstrated in no other way.

Should this procedure lead to a negative result, it may be confidently assumed that the patient is not expectorating tubercle bacilli at that time, but the sputum should be re-examined from time to time.

A large number of consumptives do not consult a physician until the disease has advanced so far that clear evidence of its existence can be obtained by these means.

Happily, however, the physician is called upon to advise many patients in an earlier stage, where the physical signs are absent or uncertain, and where the sputum contains no bacilli. In these cases early diagnosis is of supreme importance to the patient's welfare, and therefore the physician is bound to exhaust all the resources of modern medicine before giving a final opinion.

Among the recent improvements in our means of diagnosis, special reference may be made to two, namely, Calmette's ophthalmic reaction, and the opsonic index.

Calmette's Ophthalmic Reaction.—If a drop of a 1 per cent. watery suspension of dry tuberculin be placed in the normal eye, no change occurs. If, however, it be placed in the eye of a tuberculous patient, the conjunctiva becomes red and inflamed and shows all the signs and symptoms of acute muco-purulent catarrh. This reaches its maximum in about six hours and disappears completely in forty-eight hours.

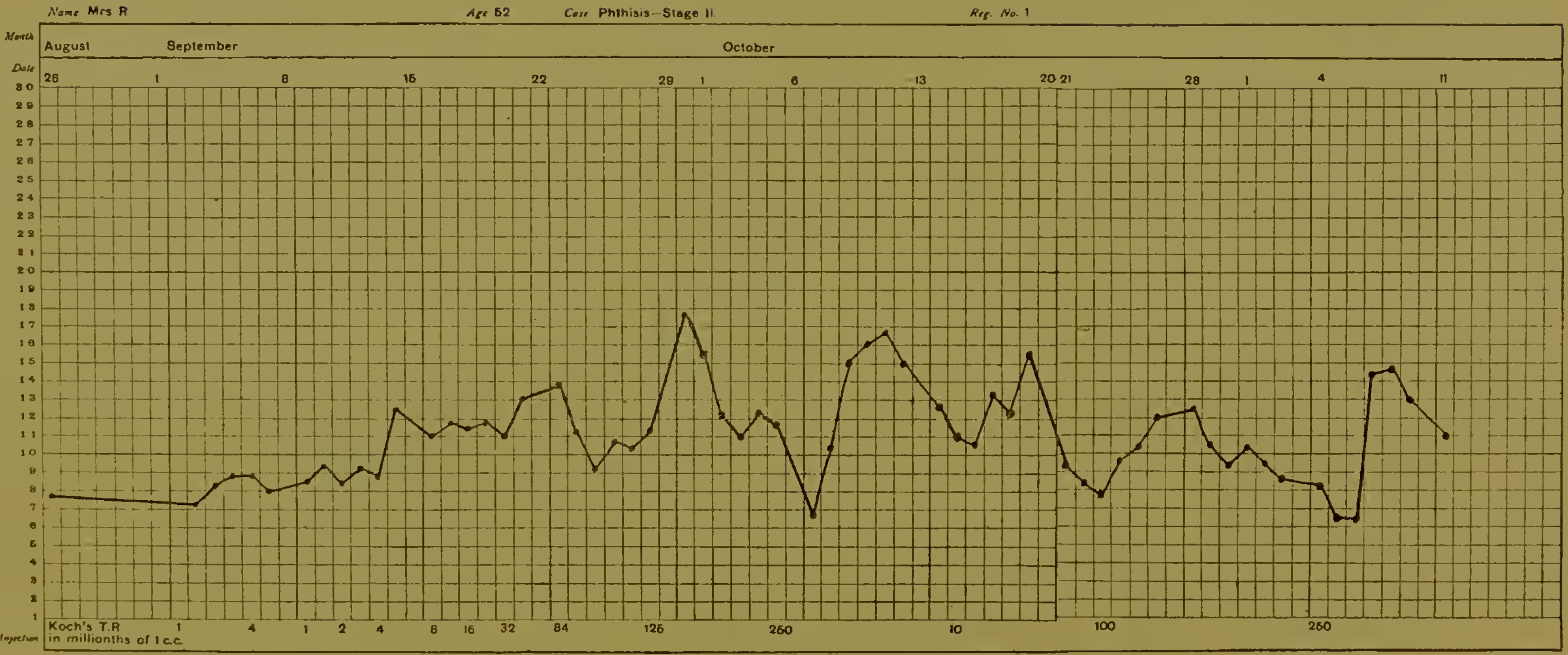


Chart I.—Showing the curve described by the opsonic index of a phthisical patient undergoing a course of tuberculin, the doses increasing in geometrical progression. It will be observed that there is a marked rise in the average height of the index. This corresponded to an equally marked improvement in the patient's general condition, all signs of active disease having disappeared.

This method is simple and easy to apply; the discomfort to the patient is slight and transient, and it is attended by not the slightest risk or danger. As to its value as a means of diagnosis there can be little doubt. In seven cases of undoubted phthisis in which we have tried it, six gave a positive result. In one case of healed lupus no reaction occurred. One case of active lupus gave it. In two gland cases one was positive. The other, a quiescent healed case, was negative.

The Opsonic Index in Diagnosis.—Where only a single estimation can be made the opsonic index may sometimes be of great value in doubtful cases. It may be assumed that in non-infected individuals the index does not vary greatly from 1·0. It has been stated that the extreme limits of variation in health are from 1·2–0·8.

We should be inclined to look with suspicion on any variation outside the narrower limits of 1·1–0·9.

A low index may be due to tubercular infection with or without auto-inoculation, or much more rarely to a natural susceptibility to the disease. The latter explanation should be accepted with great reluctance in any given case.

A normal index occurs in normal individuals, but *does not exclude* tubercular infection.

A high index occurs only in persons suffering from tuberculosis with auto-inoculation, and in those inoculated with tuberculin.

It must be borne in mind that the greater the variation from the normal index, the more certain is the diagnosis.

In our series of fifty cases of undoubted tubercular infection, we obtained the following results of the first estimation:

Index 1·1 and over	11
,, below 1·1 and over ·9 . .	10
,, ,, ·9 . . .	29

So that, taking ·9–1·1 as the possible limits of variation in health, in ten cases the index would have given no assistance in diagnosis, while in forty cases it by itself would have aroused suspicion.

Among the poorer classes, unfortunately, it is unusual for the patient to seek advice until the disease is so advanced that diagnosis is easy apart from the opsonic index, and in the great majority of our cases the estimation was made for the sake of treatment and not for diagnosis. There are cases, however, where a single index has been of great value.

For instance, a layman interested in scientific matters was in the laboratory one day, and amused himself by having his opsonic index taken. The result was so abnormal that he was advised to consult his doctor. The latter, after a very careful examination, found very uncertain physical signs at one apex, and after repeated and laborious examination of the sputum tubercle bacilli were discovered in very small numbers. In this case the diagnosis would certainly not have been made for several months but for the opsonic index.

Where the index can be taken at frequent intervals, its value in diagnosis is much greater.

A persistently low index is diagnostic of localised tubercular infection or very rarely to natural susceptibility.

A persistently normal index does not exclude tubercular infection, but makes it less probable.

A fluctuating index is diagnostic of tubercular infection, with auto-inoculation.

These maxims are confirmed by our experience. Thus, in sixteen cases of phthisis where the index was taken daily for a week, and where no inoculation was given, we found

Index persistently low	in	11	cases
Persistently normal	,,	0	,,
Fluctuating from subnormal to normal limits	,,	3	,,
,, ,, ,, hypernormal ,,	,,	2	,,

These observations were made on in-patients leading a very sedentary life, when not actually in bed. The range of fluctuation may be increased by exercise and massage and

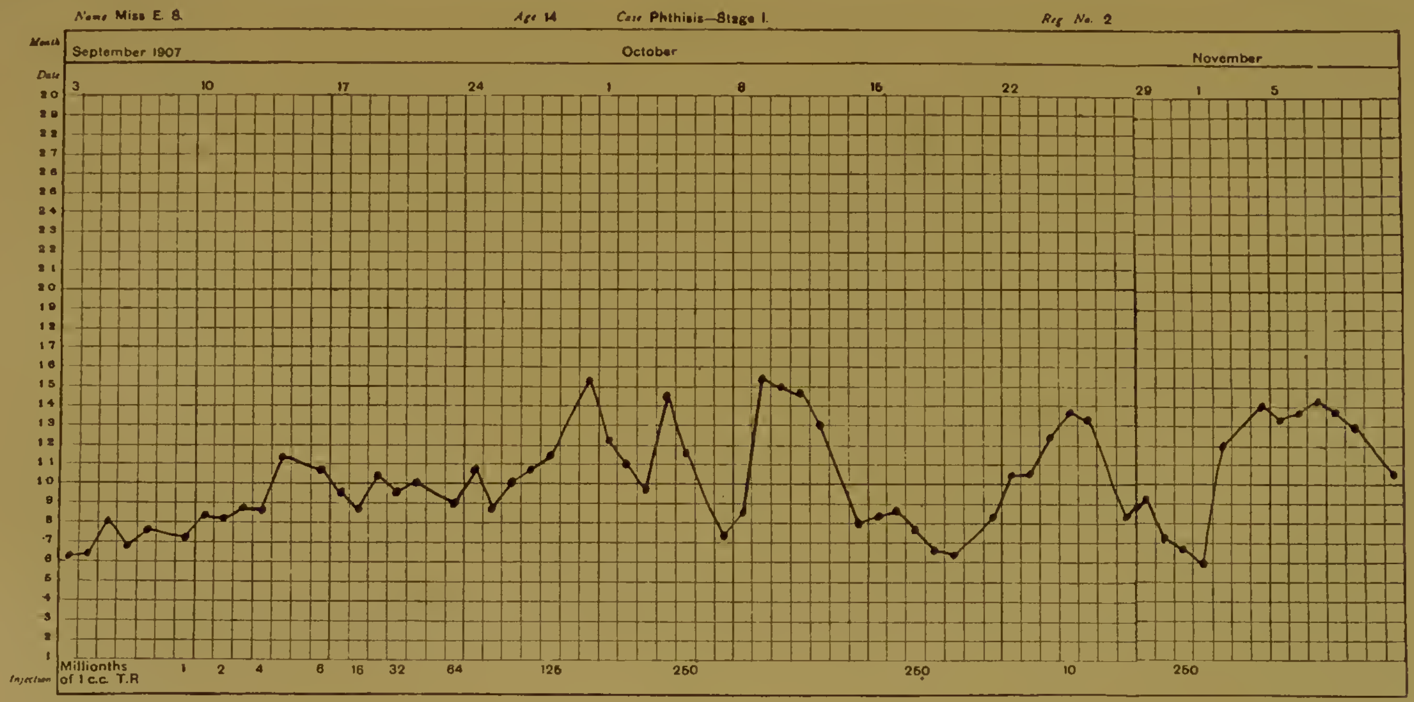
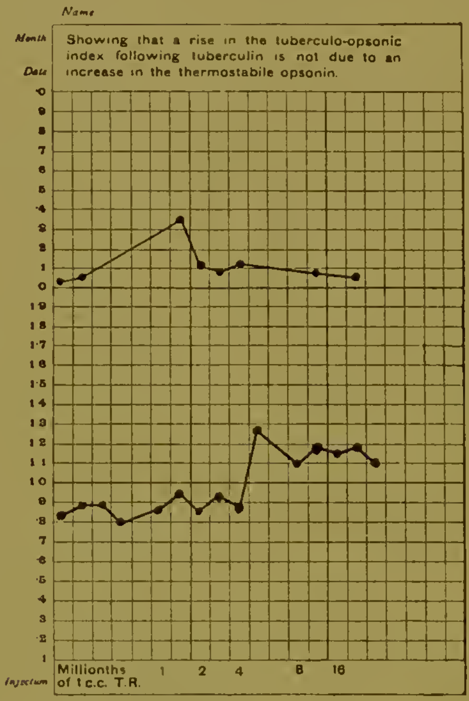


Chart II.—A practically parallel curve in the case of another patient under similar treatment. Here also all signs of active disease disappeared, and the patient was in normal health on discharge.

diminished by rest. Fluctuations so produced and controlled are pathognomonic of tubercular infection.

Heated Serum Test.—It has been confidently asserted that there are in the blood two kinds of opsonin, one destroyed by heat, and hence known as thermolabile; the other not destroyed by heat, and called thermostabile. Further, it is asserted that the thermostabile element is found in far greater abundance in tuberculous patients than in normal individuals, and thus may be used for diagnosis.



Upper line indicates the index of heated serum, the lower unheated serum

CHART III.—The upper line shows the opsonic index of the heated serum, the lower, of the unheated serum, of a patient undergoing tuberculin treatment, both indices being compared with the same unheated normal serum. It will be seen that the rise in the unheated index is not accompanied by a rise in the heated index. Hence the increase is in the thermolabile opsonins, not in the thermostabile.

To test this we examined the blood of a normal individual twelve times, of seven tuberculous subjects forty-three times. On each occasion the serum capsule was kept at 60° C. for ten minutes and its index estimated as usual, the control being unheated normal serum.

The results we obtained were as follows:—

Heated normal serum		tested	12	times	varied from	0 –·8	average	·03
Patient No	1 . .	,,	9	,,	,,	0 –·3	,,	·08
,,	2 . .	,,	8	,,	,,	·02–·35	,,	·11
,,	3 . .	,,	8	,,	,,	·02–·11	,,	·07
,,	4 . .	,,	5	,,	,,	·01–·15	,,	·08
,,	5 . .	,,	7	,,	,,	·02–·17	,,	·06
,,	6 . .	,,	3	,,	,,	·04–·08	,,	·06
,,	7 . .	,,	3	,,	,,	·02–·08	,,	·05

The average index, therefore, of heated tuberculous serum on 43 occasions was 0·07; that of heated normal serum 0·03.

It is therefore clear that the thermostabile element in tuberculous serum is usually greater than in normal serum, but may be completely absent.

On the other hand, the thermostabile element in normal serum may sometimes be greater than in tubercular serum.

We consider, therefore, that the heated serum test is of some value in diagnosis, but not much. A high thermostabile index is not inconsistent with the absence of infection, nor is a low one inconsistent with tubercular disease in an active state.

In this connection it is interesting to note that a rise in the general index produced by tuberculin, and therefore presumably specific, is not necessarily coincident with a rise in the index of the patient's heated serum.

It follows, therefore, that tuberculin produces an increase in the thermolabile opsonins, and the specific opsonins are thermolabile and not thermostabile, as has been asserted.

Some Points in the Pathology of Tuberculosis.—The tubercle bacilli having gained a foothold in any part of the body, proceed to entrench themselves by cutting off the blood supply to that part. There is thus produced a central stronghold to which the protective substances in the blood can gain admittance only through the lymph, and then but slowly and in such small quantities that they are at once absorbed by the bacilli.

Hence, whatever may be the opsonic index of the general blood-stream, that of the tubercular focus is low.

Besides living bacilli the focus of infection contains their products and dead bacilli more or less disintegrated, and these are carried into the blood-stream by means of the lymph, and affect the body generally.

The pathological indications, therefore, are to bring to bear on the site of disease the protective substances in the blood, while avoiding so far as possible the evils arising from too rapid an absorption of the poisonous substances there produced.

For obviously too rapid a circulation through the diseased focus will sweep into the circulation a large quantity of bacillary products, and will produce an excessive auto-inoculation.

Tuberculin and its Value.—Many kinds of tuberculin are on the market, and of these we have used Koch's tuberculin R. in nearly every case. We have also tried a similar preparation of the bovine bacillus. The effect seemed to be much the same as that of Koch's preparation, and as the cost is much greater, we reverted to the use of the latter. In practice we find it convenient to measure the amount of tuberculin used in whole numbers, the unit being one-millionth of one cubic centimetre of Koch's new tuberculin T.R. as sold by Messrs Meister Lucius and Brüning. The original fluid is diluted by us to form solutions of four different strengths, namely: A, 1 c.c. = 10,000; B, 1 c.c. = 1000; C, 1 c.c. = 100; D, 1 c.c. = 10; the diluent being 20 per cent. glycerine. The solutions are sterilised by heating to 60° C. for half an hour, on preparation and before and after use.

We are accustomed to inoculate on the flexor aspect of the forearm, which is washed successively with liquid soap and water, and with absolute alcohol.

The syringe is boiled before use, and the needles are kept in absolute alcohol.

If these simple precautions are taken, there is no fear of producing inflammation at the site of inoculation.

In the treatment of tuberculosis, tuberculin has now gained a recognised position, which is quite independent of the value of the opsonic index. The latter is sometimes assumed to be an index of the patient's power of resistance to the tubercle bacillus. There is some evidence to show that this is true, but it is not conclusive. It is quite conceivable that further investigation may show that the protective power of the blood is not due to the opsonins it contains, but to other substances. It may be, too, that these other substances vary independently of the opsonins, or the two may vary together in some diseases and not in others. These matters must be regarded as still *sub judice*, though we have found it useful and convenient to regard the opsonic index in tuberculosis as a true index of resistance, and our clinical observations so far confirm this view.

But whatever happens to the opsonic index, the future of tuberculin is assured. It has been in use for many years now, and its use is becoming more and more general, and with our increasing knowledge of dosage and time of administration the practical results have become so convincing that no one who has used it largely would willingly give it up.

Lupus rapidly improves under its influence, but complete disappearance of the disease requires prolonged treatment.

In one case we have had under treatment, the patient had undergone the Fensen light cure for three years, with practically no effect. Healing would take place in one part, while fresh patches broke out elsewhere.

We stopped the light treatment, and began the use of tuberculin, at the same time causing local hyperæmia by the use of a liniment containing oleate of mercury and salicylic acid. Improvement was rapid and striking for the first month, and no fresh patches occurred. This improvement has continued up to the present, though more slowly, and the patient is left with only slight scarring.

The action of Fensen light appears to be due to the production of local hyperæmia, thus flushing the diseased part with blood. The effect of this varies with the protective power of the blood. Where this is high the effect is good; where low, it may make the disease worse. If used it should be combined with tuberculin; but an equally good effect can be produced by a simple liniment.

Tubercular Glands.—Here the results of tuberculin are even more striking. In simple uncomplicated cases without sinuses and secondary infection the glands rapidly become smaller and eventually disappear. Sinus formation is effectually prevented.

One great advantage it has over operative treatment is that no scar is produced, and this alone forms an absolute indication for its use.

Where secondary infection has occurred, it may be necessary to prepare a vaccine from the other organisms present. They are usually staphylococci. In one case under our care this vaccination against secondary infection was performed accidentally with the happiest results.

Owing to an error in technique, an abscess due to staphylococci formed at the site of inoculation. This was followed by great reaction around the sinus, which discharged pus profusely. After a few days the pus became bloody, and finally the sinus completely healed up and has not since recurred. Under the influence of tuberculin the other glands became smaller, and now only two glands are palpable, whereas at the outset they were large and numerous.

Phthisis.—In this disease tuberculin is a therapeutic agent of the greatest value. It is beneficial in every case, however advanced, and does harm in none when skilfully used.

We would, however, emphasise the fact that it is an addition to our methods of treatment and not a substitute for them. It does not take the place of fresh air and good food. Rest and exercise in due season are still necessary, and it is still our duty to attend to the patient's general health and comfort.

Before administering tuberculin in any case, it is well to take the opsonic index daily for a week. During this time the patient leads a quiet life, taking his exercise in a chair out of doors. If the index fluctuates widely it may be assumed that auto-inoculation is taking place, and this must be checked. This may readily be done in most cases by keeping the patient in bed and administering Calcium lactophosphate in capsules (gr. x. quartis horis). By rest we limit the movements of the lungs, and depress the circulation, thereby checking the lymph flow through the tubercular focus, while the calcium salt produces the same result by increasing the coagulability of the blood.

In some cases it is necessary to further limit the lung movements by strapping the chest.

Having thus checked auto-inoculation, we usually begin specific treatment by injecting one unit, following this by a series of injections increasing in geometrical progression until the optimum dose is reached. The intervals between the injections is defined by a daily estimation of the opsonic index, and usually increases with the dose from two to fourteen days. The optimum dose having been reached may be repeated once a fortnight.

By administering tuberculin in this way the opsonic index is gradually raised, and this is taken to mean that the protective power of the blood as a whole is increased. It therefore only remains to flush the tubercular focus with these protective substances.

This may be done by cautiously allowing the patient to take exercise carefully graduated and by administering citric acid (gr. x. tds.). By exercise we stimulate the circulation and make the lungs move more freely, while the citric acid diminishes the coagulability of the blood. We thus encourage the flow of lymph through the site of disease.

It will be seen that the labour involved in this treatment is very great, and consequently the number is limited that one man can treat in this way. Moreover, not every patient can afford to come into the hospital for so long. We have therefore been obliged to treat many patients in the out-patient room without the advantage of an opsonic estimation. In these cases we have injected a moderate dose (usually 10 units) once a fortnight. It is not the best method, but it is the best we could do with the resources at our disposal, and it has been of great benefit to the patients. It has the great advantage that it does not interfere with the patient's employment, which is an essential point in many instances.

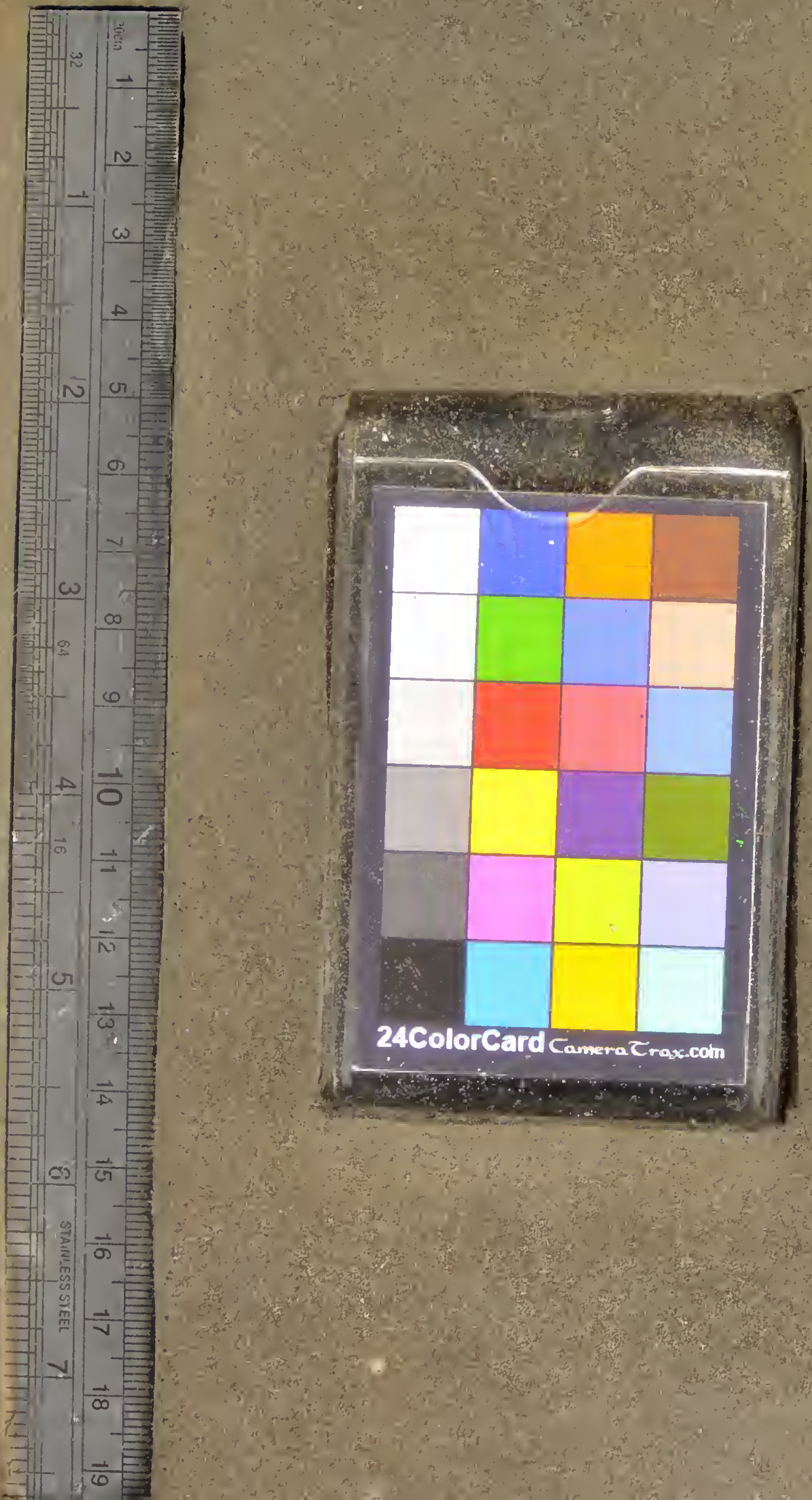
The clinical results of tuberculin are very marked. The patient invariably states that he feels better and more hopeful; sleep and digestion improve. The cough becomes less frequent and distressing, the sputum diminishes, and the patient's weight increases. The physical signs change rapidly; at first there is usually slightly increased catarrh, but this rapidly diminishes and disappears. As for the bad effects of tuberculin, we have met with none in our experience of seventy cases, and we believe that with ordinary care tuberculin can be safely given in all cases.

We are sometimes asked what class of cases are suitable for tuberculin treatment. In our opinion tuberculin is the only specific remedy we have, and should be administered in every case without exception. It must, however, be remembered that though in every case it will do some good, yet it will not always be equally successful. It may be laid down as a general rule that the prognosis is better, the earlier the treatment is undertaken, and the less extensive the area of lung involved.

The prognosis is bad where the opsonic index fluctuates and cannot be controlled by rest and drugs; also where marked secondary infection has occurred.

Tuberculin is specific and can have no effect on secondary infections, and the successful treatment of advanced phthisis depends in our opinion largely on the successful treatment of these secondary infections, by the preparation of vaccines specific against the organisms involved. This is a province of research which we hope shortly to invade and bring within the domain of practical medicine.

In conclusion, we are of opinion that in diagnosis Calmette's reaction is a valuable addition to our forces. The opsonic index is very useful in many doubtful cases, and most especially so if a series of observations be taken, though often a single observation is most highly suggestive. The heated serum test is of little value. In treatment tuberculin must be regarded as a specific of value in every case, but much depends on the skill with which it is used. And, moreover, it is used to the best advantage not as a substitute for other therapeutic measures, but in addition and supplementary to them.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